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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MEAH, MOHAMMAD Y	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,592	AFEYAN ET AL.	
	Examiner	Art Unit	
	MD. YOUNUS MEAH	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *56,110,135,137,147,150,162 and 163* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,7-9,26,27,29,31,37,48-51,58,69,70,72,74,76,78,108,117,127-129,131-134,156-161 and 164-167* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 5,7-9,26,27,29,31,37,48-51,56,58,69,70,72,74,76,78,108,110,117,127-129,131-135,137,147,150 and 156-167.

DETAILED ACTION

Claims 5, 7-9, 26-27, 29, 31, 37, 48-51, 56, 58, 69-70, 72, 74, 76, 78, 108, 110, 117, 127-129, 131-135, 137, 147, 150 and 156-167 are pending. In response to a previous non-final action mailed on 10/13/2009, Applicants on 02/17/2010 amended claims 5, 26, 29, 117, 127, 159, 161 and added new claims 164-167. Claims 56, 110, 135, 137, 147, 150 and 162-163 are withdrawn. Applicants' argue that claims 162-163 should be examined because they depend on claim 158. Applicants' argument is considered but found unpersuasive. These claims comprise use of host cell and vector comprising nucleic acid for making adzymes and as stated in prior action, belong to non-elected subject matter (group IV, see office action mailed on 8/11/05).

Applicants' arguments filed on 02/17/2010 have been fully considered but they are found unpersuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejection 35 U.S.C 112 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27, 160 remain rejected and new claim 166 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of the phrase "unstructured peptide". Any peptide would have a structure (primary- amino acid sequence) so it is unclear as to which structure is missing in an "unstructured peptide".

Applicants argue that "unstructured peptide" unstructured peptide means a protein not folded into specific structure and such term is commonly used in the scientific literature. Applicants' argument is considered but not found persuasive, because the term ""unstructured peptide" is not clearly defined in the specification and as explained above, any peptide would have a structure (primary- amino acid sequence) so it is unclear as to which structure is missing in an "unstructured peptide". If applicants mean the term means to be a protein not folded into specific structure, then the term "unstructured peptide" should be replaced by the said term.

Claim 69 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of the phrase "resistant", because the resulting claim does not set forth the metes and bound of the desired patent protection. The term "resistant" is a term of degree. It is unclear how much cleavage is required for the adzyme to be considered "resistant". The specification fails to disclose a definition of what is considered "resistant". Therefore, one of skill in the art is not able to determine the boundary of the claim.

Applicants argue that "resistant to autocatalysis" is defined in the specification and it means decrease or prevent autoproteolysis. Applicants' argument is considered but not found persuasive, because as explained above the term "resistant" is a term of degree. It is unclear how much cleavage is required for the adzyme to be considered "resistant".

Claim 157 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of the phrase "resistant", because the resulting claim does not

set forth the metes and bound of the desired patent protection. The term "resistant" is a term of degree. It is unclear how much cleavage is required for the adzyme to be considered "resistant". The specification fails to disclose a definition of what is considered "resistant". Therefore, one of skill in the art is not able to determine the boundary of the claim.

Applicants argue that "resistant to autocatalysis" is defined in the specification and it means decrease or prevent autoproteolysis. Applicants' argument is considered but not found persuasive, because the term "resistant" is a term of degree. It is unclear how much cleavage is required for the adzyme to be considered "resistant".

Claim 74 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of the phrase "adzyme inhibits biological activity of said substrate relative to...." The term is indefinite because there are many different biological activities a substrate can have which are independent from each other. If a substrate has , for example, enzymatic activity and the activity of binding to a ligand, if there is prior art that teaches an adzyme that inhibits the enzymatic activity of the substrate but not the binding activity, is the prior art adzyme encompassed by the claim? That would depend on which biological activity being considered. Correction is required.

Applicants argue that the claim recites the biological activity is the "biological activity of said substrate relative to said biological activity in the absence of said enzyme" and the claim does not differentiate between activities. Applicants' argument is

considered but found unpersuasive. As explained above there are many different biological activities a substrate can have which are independent from each other.

Claim 167 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of the phrase "adzyme inhibits bioactivity of TNFα...." The term is indefinite because TNFα can have several bioactivities such as activity of eliciting antibodies, inflammation, etc. Therefore, if the bioactivity is not defined, it is unclear as which is the TNFα bioactivity that is inhibited by the adzyme. Correction is required].

35 U.S.C 102 Rejections

Claims 5, 7-9, 37, 48-51, 58, 69-70,72, 74, 76, 78,108,127-129, 156 and 157-158 remain rejected and new claims 164-165 are rejected under 35 U.S.C. 102(b) as being anticipated by Holvoet *et al.* (JBC 1991, vol.266, pp 19717-19724). This rejection is maintained as discussed at length in the previous office action and discussed again as it relates to the new and previously rejected claims.

Holvoet *et al.* teach (page 19717 paragraph 1 and 2) fusion proteins of urokinase – a serine protease fused with a fibrin-specific antibody (variable region Fv) molecule wherein said fusion protein is made by recombinant DNA technology (FIG 1). The resulting fusion protein shows a 13-fold increase of the fibrinolytic potency. This fusion protein targets a blood clot in blood vessel, human plasma (Fig. 7, page 19722, anticipate claims 5, 7-9, 37; blood clots are component of an atherosclerotic plaque, claim 48 and 108) wherein the antibody domain binds to a fibrin and the protease

domain lyses the clot (page 19723, column 2 paragraph 2-4) via cleaving fibrin polypeptide of the blood clot. Holvoet *et al.* teach the purification of their fusion protein using a Kalikrein inhibitor (page 19719 left column 4th paragraph, anticipates claim 58). The blood clot binds an antibody in-vivo; the fusion protein alters its binding specificity and biological activity (claims 70, 74, 76, 78), and said blood clot is endogenous to a human patient (substrate, claim 7). Since the fusion protein of Holvoet et al. (comprising protease-fused with a fibrin-specific antibody (antibody is a polypeptide molecule, anticipate claim 156) is stable enough to lyse blood clot; it is resistant to autocleavage (claim 69, 129, 157). Since the fusion protein of Holvoet et al. shows a 13-fold increase of the fibrinolytic potency targets a blood clot and lyses blood clot via cleaving fibrin polypeptide, it can be used as pharmaceutical composition for the treatment of blood clot or heart disease (claims 127-129) in humans. Claims 48-51 are included in the rejection because the prior art meets all the structural limitations of the claimed invention and the additional limitations in claims 48-51 appear to be intended uses of the claimed invention. Intended use limitations do not carry patentable weight. Claims 158, 164-165 are included in the rejection because fusion protein of Holvoet *et al.* is made by recombinant DNA technology and since said fusion protein comprises a protease domain, it comprises the inherent ability to cleave peptide bond of substrate polypeptide of amyloid deposit or substrate polypeptide (claim 158) produce by pathogen or prethrombin (claim 165). Claim 164 is included in the rejection because "single polypeptide" as recited in claim 164 is interpreted as a substrate polypeptide

which is not a complex of different proteins, and fibrin of Holvoet *et al.* is not a complex of different proteins.

Argument

Applicants' argue, at pages 12-15 of their amendment of 2/17/2010 that 1) their invention is directed to adzymes where the targeting domain binds to the address site on the substrate cleaved by the protease domain and 2). Holvoet et al disclose a fusion protein where the targeting domain binds to one protein and the protease domain cleaves a different protein. Therefore Holvoet *et al.* do not anticipate applicants' invention. Applicants' arguments of their amendment of 2/17/2010 are fully considered. Applicant argument that Holvoet *et al.* do not anticipate applicants' invention are not deemed persuasive. Holvoet *et al.* teach a fusion protein of urokinase (a serine protease) fused with a fibrin-specific antibody wherein the antibody binds fibrin on a blood clot and serine protease of the fusion moiety lyses the blood clot via cleaving fibrin polypeptide (shows 13-fold increase of fibrinolytic potency, abstract). In other ward the binding domain (fibrin-specific antibody) of the fusion protein of Holvoet *et al* binds fibrin polypeptide (fibrin on the blood clot (blood clot is the substrate)) on the substrate and urokinase (a serine protease) lyses blood clot (the substrate) via cleaving fibrin polypeptide of the blood clot substrate.

CLAIM Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a)A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter

as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 117 remains rejected and new claims 165, 167 are rejected under 35 U.S.C. 103(a) by Holvoet *et al.* (JBC1991, vol.266, pp 19717-19724) or Bhatia *et al.* (Intl. J. Cancer 2000, 85, 571-577) in view of Davis *et al.* (WO 00/64485). This rejection is maintained as discussed at length in the previous office action and discussed it again.

The teachings of Holvoet *et al.* are summarized above. Holvoet *et al.* do not teach said fusion proteins comprise chymotrypsin or matrix metalloproteinase as protease.

Davis et al. teach fusion proteins made by conjugating enzymes such as chymotrypsin or matrix metalloproteinase (MMP), elastase (page 32) with targeting domain comprising ligand or substrate binding domain or protein or peptide or antibody via a linker wherein the protease catalyzes the cleavage of peptide bond of a substrate polypeptide. The chimeric protein of Davis et al. binds to the target and antagonize/inhibit /degrade a wide variety of receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc (page 28). However Davis et al made the fusion protein by chemical conjugation, not by gene fusion technique.

Bhatia *et al.* teach that production of chimeric protein by gene fusion technique have advantages over chemical conjugation, such as, tailored proteins can be made, easier to make larger quantities (page 771 column 1 3rd paragraph).

Therefore, one of ordinary skill in the art is motivated to make the protein conjugate of Davis *et al.* comprising chymotrypsin, or matrix metalloproteinase (MMP),

or elastase conjugated to antibody by gene fusion methodology as taught by Holvoet et al or Bhatia et al. and use it to inhibit bioactivity of TNF-alpha by cleaving the substrate of polypeptide cleavable by protease or metalloprotease.

As such it would have been obvious to one of ordinary skill in the art to make the fusion protein of Davis et al. by the method Bhatia et al. or Holvoet et al. and use the resulting adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate polypeptide of blood stain or tnf-alpha.

Claims 26, 27, 29, 31 remain rejected and new claims 159-161 and 166 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holvoet et al. (JBC1991, vol.266, pp 19717-19724) in view of Guo et al. (Biotech. and Bioeng. 2000, 70, 456-463). This rejection is maintained as discussed at length in the previous office action and discussed it again.

The teachings of Holvoet et al. are described above. Holvoet *et al.* do not teach use of linker in between the catalytic domain and the binding domain.

Guo et al. teach fusion proteins wherein an enzyme (ASNase) is conjugated to an immunoglobulin or fragment thereof or antibody (scFV) by a linker polypeptide $(Gly_4Ser)_3$. Guo et al also teach the advantage of $(Gly_4Ser)_3$ as a linker, such as enhanced hydrophilicity and conformational flexibility (page 457, column 1 2nd paragraph). Therefore, one of ordinary skill in the art is motivated to make a fusion protein (as taught by Holvoet et al.) wherein an enzyme (serine protease which catalyze the degradation of a specific target) is conjugated to an antibody (immunoglobulin which binds to the target) by $(Gly_4Ser)_3$ type linker.

As such it would have been obvious to one of ordinary skill in the art to make a fusion protein as taught by Holvoet et al by fusing serine protease which catalyze the degradation of a specific target to an antibody *via* a linker as taught by Guo *et al.* and use the resulting fusion protein to inactivate polypeptide substrates by catalyzing the proteolytic cleavage of the said polypeptide substrates.

Claim 51 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Holvoet *et al.* (JBC1991, vol. 266, pp 19717-19724) in view of Debburman *et al.* (PNAS 1997 94, 13938-13943). This rejection is maintained as discussed at length in the previous office action and discussed it again.

The teachings of Holvoet *et al.* are described above. Holvoet *et al* do not teach use of their fusion protein to degrade target comprising prion protein molecule.

Debburman et al. teach prion proteins comprise protease labile PrPc and protease resistant, PrPSc. Debburman et al. also teach that a protease labile prion protein converts to protease resistant, PrPSc. Protease resistant form of prion (PrPSc , page 13938 column 1, 2nd paragraph) is involved in diseases. Therefore, one of ordinary skill in the art is motivated to make fusion proteins as taught by Holvoet *et al.* comprising enzymes (protease) conjugated to binding partners wherein the binding partner is an antibody specific to a prion molecule and use it to catalyze the degradation of the prion molecule before it turn into the resistant form.

As such it would have been obvious to one of ordinary skill in the art to make a fusion protein comprising protease conjugated to prion specific antibody molecule by the method as taught by Holvoet et al and use the resulting adzyme to inactivate prion

type substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate prion polypeptides.

Claims 131-134 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Holvoet *et al.* (JBC1991, vol.266, pp 19717-19724) in view of Sanderson et al. (Medic. Res Rev 1999, Holvoet *et al.* 19, 179-197). This rejection is maintained as discussed at length in the previous office action and discussed it again.

The teachings of Holvoet *et al.* are described above.

However, Holvoet et al do not teach said a pharmaceutical preparation comprising a reversible inhibitor safe to humans.

Sanderson *et al.* (Medic. Res Rev 1999, 19, 179-197) teach a small molecule non-covalent binding protease inhibitor that used with a pharmaceutical composition which is reversible and safe in humans (abstract).

Use of protease inhibitors in a protein sample is well known in the prior art because proteases autocatalyse their own degradation (Sanderson et al). In order to extend the life of pharmaceutical preparation comprising the fusion protein and to preserve its effectiveness in humans, one of ordinary skill in the art is motivated to add a reversible protease inhibitor which is safe to humans (as taught by Sanderson et al). As such it would have been obvious to one of ordinary skill in the art to make pharmaceutical preparation comprising a fusion protein as taught by Holvoet et al and combine it with a reversible protease inhibitor as taught by Sanderson et al. so that said inhibitor is safe for humans and the pharmaceutical preparation is effective.

Argument

Applicants' arguments files on 2/17/2010 have been fully considered, but they are found unpersuasive. Applicants argument against the use of Holvoet *et al.* for not teaching the invention of claim 5 is answered in the argument against 35 USC 102 rejection above. Applicants' argue that Davis et al. chimeric protein is chemically cross-linked protein conjugate and Davis et al. especially teach the advantage of chemical cross-linking and therefore one will not motivate to use a cotranslation gene fusion technique. Bhatia et al (Intl. J. Cancer 2000, 85, 571-577, page 571, 3rd paragraph) provide motivation to make a fusion protein by gene fusion method as they teach the advantages of the recombinant fusion protein such as easier to make, a well defined product obtained, and a higher purity product compare to chemical conjugation. Thus one of ordinary skill in the art would have been **motivated** at the time of invention to make a protein conjugate comprising the protein partners of Davis et al by gene fusion methodology (as taught by Bhatia et al.) Applicants' argument against Guo et al, is considered but is not found persuasive. Guo et al provide motivation to use $(Gly_4Ser)_3$ as a linker. Guo et al teach the advantages of $(Gly_4Ser)_3$ as linker, such as enhanced hydrophilicity and conformational flexibility. Therefore, one of ordinary skill in the art is **motivated** to combine **the teachings of** Davis et al and Bhatia et al with Gao et al. The reference by Davis et al itself teaches to introduce a linker group in between the catalytic domain and the targeting domain and Guo et al, taught how to produce a protein (ASNase) conjugated to immunoglobulin (scFV) by a linker polypeptide $(Gly_4Ser)_3$. One of ordinary skill in the art can make a fusion protein by using a chimeric

gene comprising a serine protease, or MMP (as taught by Davis et al or Holvoet et al), a linker group and a targeting domain.

Double Patenting Rejection

The provisional rejection of claims 5, 7-9, 26-27, 29, 31, 35, 37, 52-53, 58, 69-70, 72, 74, 76, 78, 108, 119 and 127-29, 131-134 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-5, 19-27, 30-34, 37-41 of copending Application No.10/792498 and 10/650,591 is maintained.

Examiner agrees with applicant that the provisional double patenting rejections may be withdrawn when all claims are otherwise allowable if the copending application is not allowable. All the examined claims of the instant application are rejectable on other grounds. Since applicant did not submit terminal disclaimer, the rejections will be maintained.

Allowable Subject Matter/Conclusion

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mohammad Younus Meah
Examiner, Art Unit 1652

/Delia M. Ramirez/
Primary Examiner, Art Unit 1652